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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/523,007

02/01/2005

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1444 7590 10/15/2009  
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EXAMINER

QIAN, CELINE X

ART UNIT

PAPER NUMBER

1636

MAIL DATE

DELIVERY MODE

10/15/2009

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/523,007	<b>Applicant(s)</b> GOLDSMITH ET AL.	
	<b>Examiner</b> CELINE X. QIAN	<b>Art Unit</b> 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☐ Responsive to communication(s) filed on \_\_\_\_.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) See Continuation Sheet is/are pending in the application.
- 4a) Of the above claim(s) 66-68,72,76,77,81-83 and 87-100 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,2,4,5,7-9,11,15,16,18,23,26,28,30,36,39,43,44,49,52,54,56-60,62,80 and 102 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 01 February 2005 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_.
  3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                       | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. ____.                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>0106_0908</u> .   | 6) <input type="checkbox"/> Other: ____.                          |

Continuation of Disposition of Claims: Claims pending in the application are 1,2,4,5,7-9,11,15,16,18,23,26,28,30,36,39,43,44,49,52,54,56-60,62,66-68,72,76,77,80-83,87-100 and 102.

### **DETAILED ACTION**

Claims 1, 2, 4, 5, 7-9, 11, 15, 16, 18, 23, 26, 28, 30, 36, 39, 43, 44, 49, 52, 54, 56-60, 62, 66-68, 72, 76, 77, 80-83, 87-100 and 102 are pending in the application.

#### ***Election/Restrictions***

Applicant's election with traverse of Group I in the reply filed on 7/22/08 is acknowledged. The traversal is on the ground(s) that the invention of Groups I, II and VI all relate to the single general inventive concept of "a method of mixing genes in expression cassettes by mating the cells." Applicants assert that this linking concept is novel and patentable, over the disclosure of WO 98/31837 (US20060068472) because the reference does not relate to mating cells. Applicants thus conclude that groups I, II and VI are linked by this special technical feature.

The above argument has been fully considered but it is not found persuasive because the cited reference (WO 98/31837) does teach the concept of mixing heterologous gene expression cassettes by mating the cells. The reference discloses YAC vector comprises cloned fragments, i.e. YAC library, is transformed into competent yeast cells, and said cells are subsequently induced to mate, wherein mating results in combination between YACs bearing different inserts, and between YACs and natural yeast chromosomes (see page 63, 3<sup>rd</sup> paragraph). As such, this inventive concept is not novel in view of the teaching of WO 98/31837. Therefore, this special technical feature cannot link the invention of Groups I, II, VI as whole under PCT Rule 13.1.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, claims 66-68, 72, 76, 77, 81-83, 87-100 are withdrawn from consideration for being directed to non-elected subject matter. Claims 1, 2, 4, 5, 7-9, 11,

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15, 16, 18, 23, 26, 28, 30, 36, 39, 43, 44, 49, 52, 54, 56-60, 62, 80 and 102 are currently under examination.

***Priority***

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

***Information Disclosure Statement***

The information disclosure statements (IDS) submitted on 1/9/06 and 9/10/08 have been considered by the examiner.

***Specification***

Acknowledgment is made of Applicant's submission of the amendment to the specification and corrected sequence listing on 11/25/08.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 4, 5, 7-9, 11, 16, 18, 23, 26, 28, 30, 36, 39, 43, 44, 49, 54, 57, 59, 62 and 102 are rejected under 35 U.S.C. 102(b) as being anticipated by Delcardayre et al (WO 98/31837, see IDS).

Delcardayre et al. disclose shuffling methods using artificial chromosome in yeast (see page 62, 3<sup>rd</sup> paragraph). Delcardayre et al. disclose construction of a YAC library, comprising DNA fragments obtained from a single organism or different individual or

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species (see bridging paragraph of 62-63). Delcardayre et al. also disclose that individual genes in the library can be linked to yeast regulatory elements to form an expression cassette, and a concatemer of expression cassettes, each containing a different gene, and such concatemers are inserted into YAC (see page 63, lines 5-9). Delcardayre et al. further disclose transforming the YAC library into yeast cells, wherein the cells are induced to under meiosis, and then induced to mate, following mating, the cells are screened/selected for a desired property (see page 63, 3<sup>rd</sup> paragraph, and bridging paragraph of 63-64, and 2<sup>nd</sup> paragraph of page 64). Said process may be repeated until a desired property is acquired (see page 64, 3<sup>rd</sup> paragraph). Declardyare et al. disclose that each cell may harbor multiple YACs (page 65, line 14), and each YAC may contained two or more selectable marker (for example, a positive marker and a negative marker, see page 62, lines 24-25). Therefore, the teaching of Delcardayre et al. anticipates the claimed method of mixing heterologous genes in expression cassettes located on artificial chromosomes, comprising providing two initial population of cells that can mate with each other, each comprises at least two cells having different combinations of heterologous genes and/or expression cassettes, each cell comprises a first type of artificial chromosome comprising at least two expression cassettes comprising heterologous genes and selectable marker, selecting mated cells that carry at least a subset of the selectable markers presented in the two initial populations, and dependent claims.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 52, 56, 58 and 60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Delcardayre et al., in view of Goldsmith et al (WO 02/059296).

The teaching of Delcardayre et al. was discussed above. However, Delcardayre et al. do not teach an expression cassette comprising the general formula [rs<sub>2</sub>-SP-PR-X-TR-SP-rs<sub>1</sub>]<sub>n</sub>, wherein rs<sub>2</sub> and rs<sub>1</sub> together denote a functional restriction site, SP individually denotes a spacer of at least two nucleotide bases, PR denotes a promoter, capable of functioning in a cell, X denotes an expressible nucleotide sequence, TR denotes a terminator, and n>=2, or n>=10, and wherein at least a first cassette is different from a second cassette, and essentially all cassette are recognized by the same restriction

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enzyme, and wherein the expression cassette also comprises an intron between the promoter and the expressible nucleotide sequence.

Goldsmith et al. teach methods and vectors for cloning large numbers of expressible nucleotide sequence adapted for random ligation into concatemers, and inserting said nucleotide sequences into an expression host for expression of the genes in the concatemer or a subset of genes in the concatemer. Goldsmith et al. teach that such expression cassette may be optimized to express nucleotide for any screenable trait (see page 3, lines 23-29). Goldsmith et al. further teach the concatemer comprises the general formula  $[rs_2\text{-}SP\text{-}PR\text{-}X\text{-}TR\text{-}SP\text{-}rs_1]_n$ , wherein  $rs_2$  and  $rs_1$  together denote a functional restriction site, SP individually denotes a spacer of at least two nucleotide bases, PR denotes a promoter, capable of functioning in a cell, X denotes an expressible nucleotide sequence, TR denotes a terminator, and  $n \geq 2$  and wherein at least a first cassette is different from a second cassette. Goldsmith et al. assert that the advantage of the concatemers is the expression cassettes can be cut out from the concatemers at any point to make new combinations of expression cassette, and the cassette can be recovered from the host cell through nucleotide isolation and subsequent digestion with a restriction enzyme specific for the rs site. Goldsmith et al. also teach that intron sequences may be included in said cassette at 5' or 3' of the expressible nucleotide sequences.

It would have been obvious to an ordinary skill in the art to make concatemers comprising the general formula taught by Goldsmith et al. and insert into the artificial chromosome to be mixed by mating the host cell and selecting a desired trait based on the teaching of Delcardayre et al. Delcardayre et al. teach the claimed method of mixing heterologous gene in expression cassette located on artificial chromosome, and indicates



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YACs comprising concatemers of expression cassettes that comprises different combination of genes and regulatory sequences may be used for this method. It would have been obvious to an ordinary artisan to construct the concatemer expression cassettes according to the teaching of Goldsmith because the advantage of including different combination of genes and recovering said combination of genes is desired in the method taught by Delcardayre et al. It would also have been obvious to an ordinary artisan to varying the number of concatemers to at least 2 copies or 10 copies based on the need because it is contemplated by the teaching of Goldsmith et al. Moreover, it would have been obvious to an ordinary artisan to include an intron in the expression cassette as suggested by Goldsmith for the desired intonic effect such as splicing in a particular host. Combining the prior art methods to achieve the predictable result is within the knowledge of an ordinary skill in the art. Therefore, the claimed invention would have been *prima facie* obvious to the ordinary artisan at the time the invention was made.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4, 5, 7-9, 11, 15, 16, 18, 23, 26, 28, 30, 36, 39, 43, 44, 49, 52, 54, 56-60, 62, 80 and 102 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the claimed method using yeast or fungal cells as host, does not reasonably provide enablement for the claimed method in other cell types such as mammalian, vertebrate, plant, insect cells. The specification does not enable any

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person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

**The nature of the invention:**

The claimed invention is drawn to a method of mixing heterologous genes in expression cassettes located on artificial chromosomes, comprising providing two initial population of cells that can mate with each other, each comprises at least two cells having different combinations of heterologous genes and/or expression cassettes, each cell comprises a first type of artificial chromosome comprising at least two expression cassettes comprising heterologous genes and selectable marker, selecting mated cells that carry at least a subset of the selectable markers presented in the two initial populations.

**The breadth of the claim and the teaching of the specification:**

The breadth of the claim with regard to the host cell, the initial cell population that comprises artificial chromosomes, in the context of the claimed method is broad. It encompasses any type of cell including eukaryotic cell such as mammalian, vertebrate,

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invertebrate animals, plants, insect, and prokaryotic cells, etc. However, mixing heterologous expression cassettes located on artificial chromosome through the process of mating do not occur for mammalian, vertebrate, invertebrate, plant and insect cells. For prokaryotic cells such as bacteria, "mating," a process of equal exchange of genetic material or fusing of gametes and creation of a zygote, does not occur. Even if bacterial conjugation is considered "mating," it does not involve meiosis and mixing spores as contemplated by the claimed invention. The specification does not provide guidance for practicing the claimed method in host cells other than yeast or fungal cells. Therefore, the breadth of the claim exceeds the teaching of the specification.

**The state of prior art and the predictability in the art:**

The state of art at the time of filing does not provide teaching for how to accomplish the mating for the purpose of mixing heterologous gene cassettes located on the artificial chromosome and subsequent selection and meiosis in cells other than yeast and fungal species. In fact, the art teaches that the exchange of genetic material between cells such as mammalian, plant, insect, etc occurs through mechanism other than "mating." As such, whether the claimed method can be practiced with any type of cell is unpredictable. Without teaching from the specification and prior art, one skilled in the art would have to engage in undue experimentation to practice the claimed method to its full scope. Therefore, the claimed invention is only enabled to the scope as indicated above.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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Claims 4, 8, 9, 15, 16, 43, 52, 54, 56, 57, 58, 60, 62 and 80 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claim 4, the recitation of "at least one marker from and artificial chromosome in each of the initial population..." renders the claim indefinite because it is unclear where this marker is from.

Claim 8 recites the limitation "screening cells that undergone meiosis" in lines 2-3. There is insufficient antecedent basis for this limitation in the claim because claim 1 does not recite any cell that undergoes meiosis. Claim 9 is also rejected for the same reason because it depends on claim 8.

Claim 15 recites the limitation "after meiosis" in line 3. There is insufficient antecedent basis for this limitation in the claim because claim 1 does not recite any cell undergoes meiosis.

Claim 16 recites the limitation "mixing spores" in line 2. There is insufficient antecedent basis for this limitation in the claim because claim 1 does not recite any spores.

Regarding claim 43, the recitation of "wherein the species of cells is fungal cells selected from a spore forming species" renders the claim indefinite because it is unclear what the choices for selection are. In other words, to select something, it must have more than one thing to select from. The claim only gives one option of spore forming species. As such, it is unclear what the metes and bounds of this claim is.

Regarding claim 52, the recitation of "rs1 and rs2 together denotes a functional restriction site" renders the claim indefinite because it is unclear what rs1 or rs2 stands

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for individually. In other words, rs1 and rs2 are at opposite ends of the formula, and it is unclear what each of them stands for (they are not together). It is noted that the limitation of "SP individually denotes..." is recited twice, and is redundant. Claims 56, 58, 60 and 62 are rejected for same reason because they depend on claim 52.

Regarding claim 54, the term "expression states" renders the claim indefinite because the meaning of this term is unclear in the context of nucleotide sequence as recited.

Regarding claim 56, the term "essentially all" renders the claim indefinite because it is unclear what percentage of the cassette is encompassed by this term.

Regarding claim 57, the term "substantially all" renders the claim indefinite because it is unclear what percentage of the cassette is encompassed by this term.

Regarding claim 62, the term "wherein the different expression state represent at least two different tissues..." renders the claim indefinite because it is unclear how the expression state may be represented by tissue, etc. Moreover, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05.

Claim 80 recites the limitation "for every 2-3 rounds of meiosis and selection" in 4-5. There is insufficient antecedent basis for this limitation in the claim because claim recites neither meiosis, nor 2-3 rounds of selection and meiosis.

No claims are allowed.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to CELINE X. QIAN whose telephone number is (571)272-0777. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Celine X Qian /  
Primary Examiner, Art Unit 1636

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